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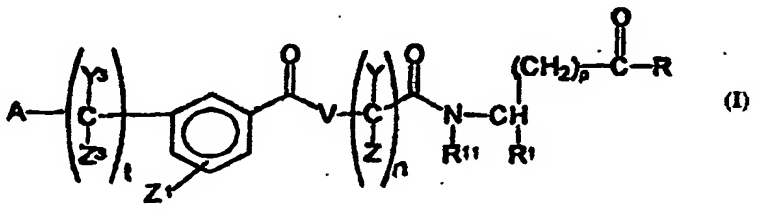
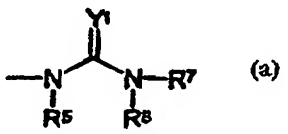
(54) Title: META-GUANIDINE, UREA, THIOUREA OR AZACYCLIC AMINO BENZOIC ACID DERIVATIVES AS INTEGRIN ANTAGONISTS

(57) Abstract

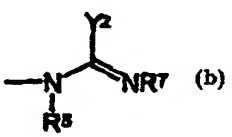
The present invention relates to a class of compounds represented by formula (I) or a pharmaceutically acceptable salt thereof, wherein A is (a) or (b) or (c) or (d) pharmaceutical compositions thereof and methods of using such compounds and compositions as $\alpha_v\beta_3$ integrin antagonists.



(I)



(a)



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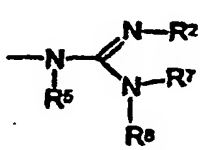

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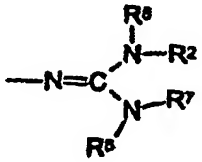


(d)

META-GUANIDINE, UREA, THIOUREA OR AZACYCLIC AMINO BENZOIC ACID DERIVATIVES AS INTEGRIN ANTAGONISTS

The present application claims priority under 35 USC §119(e) of United States provisional application Serial No. 60/003,277 filed August 30, 1995.

Field of the Invention

The present invention relates to pharmaceutical agents (compounds) which are useful as $\alpha_v\beta_3$ integrin antagonists and as such are useful in pharmaceutical compositions and in methods for treating conditions mediated by $\alpha_v\beta_3$ by inhibiting or antagonizing $\alpha_v\beta_3$ integrins.

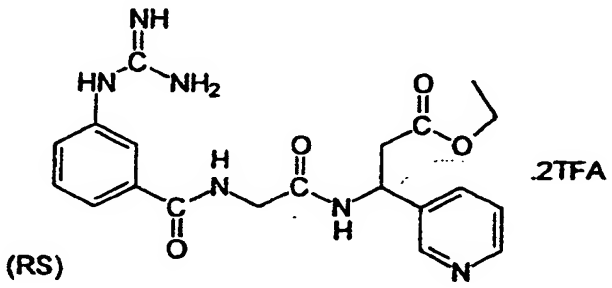
Background of the Invention

Integrins are a group of cell surface glycoproteins which mediate cell adhesion and therefore are useful mediators of cell adhesion interactions which occur during various biological processes. Integrins are heterodimers composed of noncovalently linked α and β polypeptide subunits. Currently eleven different α subunits have been identified and six different β subunits have been identified. The various α subunits can combine with various β subunits to form distinct integrins.

The integrin identified as $\alpha_v\beta_3$ (also known as the vitronectin receptor) has been identified as an integrin which plays a role in various conditions or disease states including tumor metastasis, solid tumor growth (neoplasia), osteoporosis, Paget's disease, humoral hypercalcemia of malignancy, angiogenesis, including tumor angiogenesis, retinopathy, arthritis, including rheumatoid arthritis, periodontal disease, psoriasis and smooth muscle cell migration (e.g. restenosis). Additionally, it has been found that such agents would be useful as antivirals, antifungals and antimicrobials. Thus, compounds which selectively

Example 1

Preparation of (±)ethyl β-[[2-[[[3-[(aminoiminomethyl)-amino]phenyl]carbonyl]amino]acetyl]amino]pyridine-3-propanoate, bis(trifluoroacetate) salt



Step A

To 3-pyridine carboxaldehyde (300 ml) in 2-propanol (3 liters) was added ammonium acetate (297 g) followed by malonic acid (398 g). The reaction mixture was stirred at reflux for 5 hours. The precipitate was filtered while hot and washed with hot isopropanol (2 liters). The resulting white solid was then dried to yield DL-3-amino-3-(3-pyridyl)propionic acid (220 g) as a white solid.

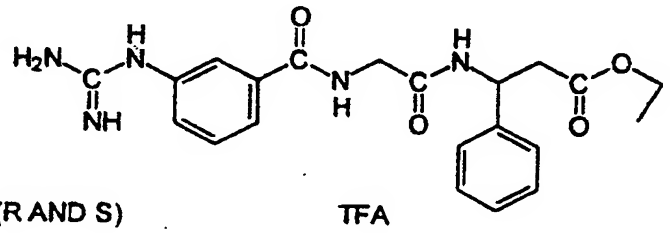
NMR and MS were consistent with the desired product.

Step B

DL-3-amino-3-(3-pyridyl)propionic acid (220 g) from Step A was slurried in absolute EtOH (3.6 liters). HCl gas (one lecture bottle - ½ lb) was bubbled into the reaction while stirring over 40 minutes (slow exotherm to 61°C). The slurry was then heated at reflux for 4 hours (a solution forms after 1 to 1.5 hours). The reaction mixture was cooled to 5°C in an ice bath. After stirring at 5°C for 1.5 hours, the resulting white precipitate was filtered and washed thoroughly with ether. After drying under vacuum at 50°C, the yield of ethyl DL-3-amino-3-(3-

Example 3

Preparation of (±)ethyl β-[[2-[[[3-[(aminoiminomethyl)-amino]phenyl]carbonyl]amino]acetyl]amino]-benzenepropanoate, trifluoroacetate salt



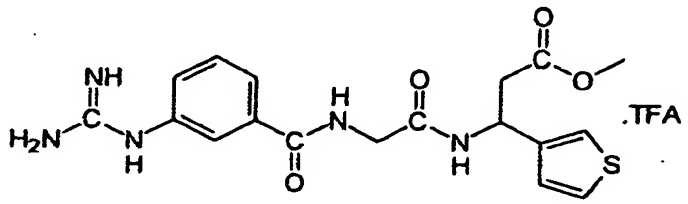
(R AND S) TFA

The above compound was prepared according to the methodology of Example 1, substituting an equivalent amount of benzaldehyde for 3-pyridinecarboxaldehyde in Step A.

NMR and MS were consistent with the desired structure.

Example 57

Preparation of (±) methyl β-[[2-[[[3-[(aminoiminomethyl)amino]phenyl]carbonyl]amino]acetyl]-amino]thiophene-3-propanoate, trifluoroacetate salt



Step A

A solution of 3-thiophenecarboxaldehyde (11.2 g) in isopropanol (100 ml) was treated with ammonium acetate (20 g). The resulting mixture was heated and malonic acid (10.4 g) was added. The reaction was refluxed for 4 hours and filtered while hot. The solid was washed with hot isopropanol (2 x 50 ml) and dried *in vacuo* overnight at 40°C. 8 g of β-aminothiophene-3-propanoic acid was recovered. MS and ^{1}H-NMR were consistent with the desired product.

Step B

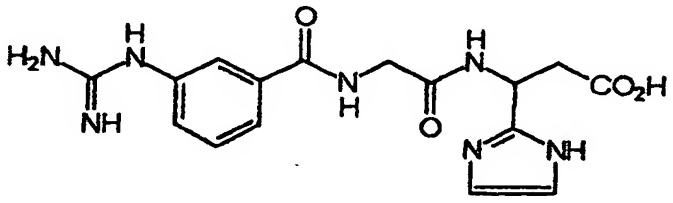
A suspension of the product of Step A (5 g) in methanol (100 ml) was treated with 4N HCl/dioxane (10 ml). The reaction was stirred overnight. The excess solvent was removed under reduced pressure. Methyl β-aminothiophene-3-propanoate hydrochloride (7.8 g) was isolated as a yellow foam. MS and ^{1}H-NMR were consistent with the desired product.

Step C

A solution of m-guanidinohippuric acid HCl (2.7 g) in DMF (10 ml) and pyridine (10 ml) was treated with DSC (4.5 g) and a catalytic amount of DMAP. After 4 hours, a solution of the product of Step B (2.2 g) and

Example 364

Preparation of (±) β-[[2-[[[3-[(aminoiminomethyl)-amino]phenyl]carbonyl]amino]acetyl]amino]-1H-imidazole-2-propanoic acid, tris(trifluoroacetate) salt



Step A

A solution of 2-imidazolecarboxaldehyde (6.0 g, 0.063 mol) and (tert-butylcarbonylmethylene)triphenylphosphorane (29.4 g, 0.078 mol) in 150 mL of tetrahydrofuran was heated at 55°C overnight. The clear solution was cooled and concentrated *in vacuo*. The residue was purified by chromatography on silica gel (ethyl acetate/hexane, 8:2) to give 9.7 g of product (1:1 E/Z mixture) as a white solid (79%): Analysis Calc'd. for $C_{10}H_{14}N_2O_2$:

C, 61.84; H, 7.27; N, 14.42.

Found: C, 61.52; H, 7.39; N, 14.21.

Step B

To a suspension of prewashed sodium hydride (0.62 g, 0.026 mol) in 40 mL of dry dimethylformamide was added the product from Step A slowly. After 30 minutes, 2-(trimethylsilyl)ethoxymethyl chloride was added and the reaction mixture was stirred at room temperature for 2 hours. Water was added and the aqueous phase was extracted with ethyl acetate. The organic layer was washed with brine, dried over magnesium sulfate and filtered. The filtrate was concentrated and the residue